REMARKS

Reconsideration of the subject patent application is respectfully requested.

Claims 50-55 and 61-63 are currently pending and these nine (9) claims have been rejected based on one or more prior art references cited by the Examiner in the August 18, 2010 non-final Office Action. More specifically, claims 50-55 and 63 stand rejected under 35 U.S.C. §102(b) as being anticipated by Hainfeld et al. Claims 50-55, 61, and 62 are rejected under 35 U.S.C. §102(b) as being anticipated by Peschel et al. as evidenced by Rembaum. Claims 1-49 and 56-60 have been canceled. In response to these most recent claim rejections, claims 50-55 and 61-63 have been amended as reflected in this Response.

Briefly, the inventive subject matter, as recited in the claims, is directed to a pharmaceutical composition for the therapeutic treatment of neoplastic and cancerous disorders of the human or animal body, wherein the composition as such comprises the respective metal cluster nanocompound as well as a pharmaceutically tolerated, non-toxic excipient. In this context, it is noted that the recited pharmaceutical composition is formulated for the therapeutic treatment of neoplastic and cancerous disorders of the human or animal body. Further, the metal cluster nanocompound of transition metals as used with respect to the pharmaceutical composition has been defined such that the respective ligands L' are selected from the group consisting of $P(C_6H_5)_2(C_6H_4SO_3H)$ and $P(C_6H_5)H_2(meta\text{-}C_6H_4SO_3H)$. In this context, the inventive embodiment according to

which the respective ligand L' is represented by a triphenylphosphine radical has been deleted from claims 50 and 63.

The subject patent application provides a fairly detailed background discussion regarding neoplastic and cancerous diseases and conventional treatment theories and options. One of those options, the use of cisplatin, is specifically discussed. There are, however, significant issues and concerns with this treatment option as explained on page 3, lines 17-39, and page 4, lines 1-12, of the specification. A portion of the specification is reproduced below for emphasis and as a reminder with regard to these issues and concerns regarding prior art treatment options.

> In the case of most cancer or tumor cells, the above-described protective mechanism is no longer in force in the course of degeneration. It is therefore the aim of many therapeutic approaches to inhibit or to end growth or division of tumor or cancer cells, in particular to induce possibly blocking or even destruction of the tumor or cancer cell DNA. For this purpose, for example, platinum or ruthenium metal compounds, such as, for example, cis-diaminodichloroplatinum(II) ("cisplatin"), are used.
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> Interactions between metals and biological macromolecules, including proteins, polysaccharides and nucleic acids, are of particular interest, since they are crucially important to a multiplicity of natural and technical processes. These processes range from interactions between

highly specific metal cofactors with particular proteins to biosorption of heavy metals by polysaccharide hydrogels.

The unique properties of DNA have resulted in the development of new materials, in particular in the field of medicine. However, conventional antitumor research is essentially focused on the interactions between platinum- and ruthenium-containing compounds with the major grooves and minor grooves of polynucleotides.

However, some of the previously used compounds have serious side effects. Thus, for example, cisplatin which binds to guanine of DNA and RNA is known to possess extreme nephrotoxicity which, in the worst case, can even result in necroses. There are furthermore a number of cisplatin-resistant tumors which are not accessible to a therapy with cisplatin.

The focus of the claimed invention, as recited in amended claims 50 and 63, is to identify and selectively formulate a "suitable" pharmaceutical composition which resolves, or at least ameliorates, the disadvantages and drawbacks with the prior art treatment options. The claimed invention should not be trivialized as the Examiner seems to be doing by the contention that the "invention" is limited to a recognition of a possible therapeutic use of an existing composition. The elements recited in claims 50 and 63 are directed to a purposeful selection and combination of properties and parameters for the recited pharmaceutical composition such as the presence of

physiologically tolerated salts, the electronegativity, the stabilization energy, and the specific ligand molecular formulation.

With respect to the inventive concept, the inventors have surprisingly found that compositions of very specific metal cluster nanocompounds exhibit a high therapeutic effect with respect to the treatment of neoplastic and cancerous diseases. In this context, the inventors have surprisingly found out that the respective metal cluster nanocompounds having very specific ligands are able to interact under particular preconditions with the DNA, in particular B-DNA, of human or animal cells, in particular of tumor or cancer cells, under physiological conditions. Thus, one central gist of the claimed invention has to be seen in the provision of a pharmaceutical composition for the treatment of cancerous disorders comprising specific metal cluster nanocompounds being specifically tailored to interact with DNA of cancer and/or tumor cells which results in a destruction of the respective cancer and/or tumor cells.

The claimed pharmaceutical composition provides certain advantages and this fact is a further indication of its patentability over the cited prior art.

For example, the inventive pharmaceutical compositions comprising the very specific metal cluster nanocompounds were found to be capable of inhibiting or halting the growth and division of tumor and cancer cells, even of inducing destruction of the tumor- and cancer-cell DNA (page 16, lines 12 to 18 of the specification).

The inventive pharmaceutical compositions comprising the respective metal cluster nanocompounds were found to be particularly effective in in-vitro studies, even on cisplatin-resistant tumors. In comparison with cisplatin, a distinctly improved

efficiency was found in the treatment of tumors which are not resistant to cisplatin (page 16, lines 20 to 26 of the specification).

It is assumed, without being committed to a particular theory, that the metal cluster nanocompounds used according to the invention are deposited in the major grooves of the DNA, in particular B-DNA, of tumor or cancer cells and are capable of interacting there with the DNA (page 16, lines 28 to 33 of the specification). In this context, the inventors have also found that compounds having an inner AU_{55}-core and in particular the AU_{55}-core compounds with sulfonated ligands on the basis of $[AU_{55}\{P(C_6H_5)_2(C_6H_4SO_3H)\}_{12}Cl_6]$ and $[AU_{55}\{P(C_6H_5)_2\,(meta\text{-}C_6H_4SO_3H)\}_{12}\,Cl_6]$ are particularly effective in this context. Studies by the inventors have found that the free acid has an even stronger pharmaceutical potential or superior efficiency in comparison with the corresponding alkali sulfonate. Without being committed to a particular theory, the efficiency of these compounds can possibly be explained by the fact that they interact with the GDA base sequences of the DNA in question (paragraph bridging pages 16/17 of the specification). In this context, reference is also made to the example embodiments as delineated on page 21 to 28 of the specification. On the whole, the respective experiments and studies by the inventors show the high efficiency especially of the specific metal cluster nanocompounds on the basis of the respective sulfonated ligands which form the basis for the inventive pharmaceutical composition according to newly amended claims 50 and 63.

On the whole, the claimed invention refers to a pharmaceutical composition being specifically optimized for the purpose of the specific therapeutic treatment of neoplastic and cancerous disorders of the human or animal body, wherein the claimed

pharmaceutical composition comprises very specific metal cluster nanocompounds on the basis of an AU_{55}-core with very specific ligands on the basis of sulfonated derivatives of triphenylphosphine. The respective new therapeutic use of the metal cluster nanocompound as such is neither disclosed nor rendered obvious on the basis of the prior art documents and clearly represents an efficient delimitation over the prior art.

The Examiner has taken the position that Hainfeld et al. provides a basis to reject claims 50-55 and 63 based on some theory of inherency according to MPEP §2112, I and II. The Examiner's premise for this rejection is that Applicants have merely discovered a previously-unappreciated property of a prior art composition. Whether or not there is an "inherent teaching" in the recited prior art reference is a question of fact. Further, the only issue addressed by the referenced MPEP section is whether the "old composition" has been found to have a new use.

The Examiner references $Au_{55}\{PPh_3\}_{12}Cl_6$ which is discussed in Example 16 of Hainfeld et al. However, this composition is different from what Applicants recite in claims 50 and 63 for the ligand (L') portion of Applicants' formulation. Claims 50 and 63 has been amended to delete the recitations to the triphenylphosphine radial and to derivates of triphenylphosphine. What is left for the L' ligand options are specific formulations which do not correspond to any of the compositions or formulations disclosed in Hainfeld et al. MPEP §2112 is limited to what might be inherent in an "old composition". As such a specific and purposeful new composition, which is not found in the cited prior art, is eligible for and entitled to a favorable patentability determination.

In this regard, it is important to recognize not only the unique complexity of the specific formulation and how it will interact with the subjects' DNA under physiological

conditions, but it is also important to recognize and acknowledge the complexities and "mysteries" of the DNA double helix. The claimed invention is a specific metal cluster nanocompound with the specific formulation and composition which has been found to have a unique and beneficial application in the treatment of neoplastic and cancerous disorders. Whether or not a completely different prior art composition might have a medical application is irrelevant to the issue of patentability for the specific composition recited in Applicants' claims.

Further, and more specifically, the present invention deals with a pharmaceutical composition comprising very specific metal cluster nanocompounds, wherein the inventive pharmaceutical composition is purposefully optimized and formulated for the therapeutic treatment of neoplastic and cancerous disorders of the human or animal body. It is pointed out that the specific effectiveness of the metal cluster nanocompounds as such has never been recognized or considered on the basis of the prior art documents. The amended claims are in condition for allowance relative to Hainfeld et al. as this cited reference does not disclose the recited metal cluster nanocompounds. In this context, reference is made to the inventive Examples, especially to Example 4 on pages 26 to 28 of the specification wherein the in vitro cytotoxicity of the metal cluster nanocompound $[AU_{55}\{P(C_6H_5)_2(C_6H_4SO_3H)\}_{12}Cl_6]$ and thus of an AU_{55}-complex with the further specified monosulfonated triphenylphosphine ligands has been investigated.

In this context, a very high efficiency against the respective tumor cells has been surprisingly found out. In this context, it is explicitly delineated in the second complete paragraph on page 27 (lines 10 to 22) of the specification as reproduced below:

For the cell lines studied, [AU_{55}] was generally found to have faster and higher cytotoxicity than cisplatin, as is apparent from the IC_{50} data in table 2. The only previously tested healthy cells, namely those of MC3, characteristically respond more weakly to [AU_{55}] than the bone tumor cells U20S. This leads to the conclusion that [AU_{55}] is less toxic to healthy cells than to tumor cells. Experiments with healthy skin cells and tumor skin cells (melanoma) show the same tendency. Also remarkable is the fact that metastatic melanoma cells are resistant to cisplatin but extremely sensitive to [AU_{55}]. Thus, there is the possibility of applying [AU_{55}] particularly in case in which resistance of cisplatin occurs.

Based on page 6, lines 6-9, the [Au_{55}] reference is $AU_{55}\{P(C_6H_5)_2(C_6H_4SO_3H)\}_{12}Cl_6$, as recited in the claims.

Hainfeld et al. refers to antibody-gold cluster conjugates wherein the antibody is covalently bonded to the cluster, resulting per se in completely different compositions.

As to the amendments now performed with respect to amended claims 50 and 63 with the further specification of the ligands used for the AU_{55}-core, it is to be pointed out that Hainfeld et al. does not disclose the specific metal cluster nanocompounds as used for the inventive pharmaceutical composition comprising very specific sulfonated triphenylphosphines comprising a specific sulfone group. For, in contrast to the claimed invention, Hainfeld et al. only refers to unmodified triphenylphosphines as the respective

radicals, and this, furthermore, also in the sense of starting materials for the subsequent synthesis of a different end product being in the monomaleimide form of the respective triphenylphosphines, the latter presenting the main focus of the Hainfeld et al. reference. For, it is the specific maleimide group which is to react with sulfhydryl groups in order to covalently bond the respective antibody to the core (see column 9, lines 52 to 57 of Hainfeld et al.). Thus, on the whole, Hainfeld et al. has nothing in common with respect to the specific metal cluster nanocompounds having sulfonated triphenylphosphines ligands which, however, surprisingly results in the high efficiency of the inventive compounds with respect to the treatment of cancerous diseases.

Hainfeld et al. does not inherently disclose any pharmaceutical efficiency in the sense of the claimed invention, especially since at least (i) different metal cluster nanocompounds are used, (ii) the different metal cluster nanocompounds are conjugated to antibodies, (iii) the specific conjugates of Hainfeld et al. are not able at all to interact with DNA in the sense of the claimed invention and (iv) a completely different pharmaceutical approach is realized due to the use of radiation exposure or the use of radioactive gold isotopes.

With regard to the rejection of claims 50-55, 61, and 62 based on Peschel et al., as evidenced by Rembaum, Peschel et al. refers to the preparation of monolayers of ligand-stabilized gold-clusters on a poly(ethyleneimine) coated carrier.

Peschel et al. has nothing in common with any medical application of gold-clusters as such and only refers to the field of nanotechnology and especially to quantum dots, wherein one main focus of Peschel et al. is based on the realization of a highly ordered two-dimensional arrangement of chemically produced quantum dots. In this

context, specific metal cluster nanocompounds are fixed on a layered structure comprising a thin layer of poly(ethyleneimine) wherein the metal cluster nanocompounds are covalently attached to the poly(ethyleneimine) layer in order to provide a two-dimensional highly ordered arrangement of the respective metal cluster nanocompound.

Peschel et al. does not allow for any interpretation that the respective complex described in this reference would be appropriate for medical uses and even more for a therapeutic use as to cancerous diseases. For, as delineated above, according to Peschel et al., the metal cluster nanocompounds are compulsorily fixed onto a layered structure comprising a poly(ethyleneimine) layer which makes the complex according to Peschel et al. completely inappropriate to be used as a pharmaceutical composition with the application to a human or animal. In fact, the skilled practitioner would never consider applying the two-dimensional complex with the respective metal cluster nanocompounds being chemically fixed onto a film for medical uses.

The fixation of the metal cluster nanocompounds onto a layered structure with the new steric arrangement of the complexes onto the underlying film would even contravene the purposeful interaction of the complexes with DNA within the human or animal body since the highly ordered structure would not optimally fit to the DNA target. Consequently, due to the ordered structure and fixation onto a layer, any interaction with a DNA molecule would be drastically hindered or even disabled. This applies even more since the layered construction as such would not able to be introduced into a cancer or tumor cell and into the cell nucleus in order to interact with the respective DNA. Thus, the specific layered structure with the covalent attachment of the metal cluster nanocompounds on the basis of the two-dimensional and plane structure does not allow

for any specific medical use of the structure as such. Further, Peschel et al. does not allow for the interpretation of a pharmacologic effect in accordance with the claimed invention.

With regard to Rembaum, Applicants disagree with the Examiner's interpretation and application of this reference as part of this rejection. The Examiner seems to be of the opinion that a person of ordinary skill in the art would have recognized that formulating an active agent with polyethyleneimine is an appropriate formulation for cancer treatment so that on the basis of this assumption this hypothetical person would directly take into consideration a medical use of the composition described in Peschel et al. Applicants disagree as this theory is not consistent with medical expert knowledge. First, Rembaum refers to completely different pharmacologically active compounds on the basis of specific ionene polymers, especially ionene bromide, and thus to specific polyquarternary polymers, which, however, refer to a completely different class of substances and can therefore not at all be compared with the specific metal cluster nanocompounds. On the other hand, the mere facultative use of polyethyleneimine, as delineated in Rembaum, only refers to the polycation thereof as such and not at all to a specific arrangement of polyethyleneimine in the form of a layer as compulsorily realized according to Peschel et al. Therefore, the assessment of the Examiner with respect to the Rembaum reference and its pertinence with regard to does not hold true.

Considering the amendments made to each of the pending claims and considering Applicants' remarks, technical explanations, and arguments as set forth above, claims 50-55 and 61-63 are in condition for allowance and such action by the Examiner is respectfully requested.

Respectfully submitted,

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